PB88-178751

Health and Environmental Effects Profile for 4,4′-Methylenediphenylisocyanate

(U.S.) Environmental Protection Agency
Cincinnati, OH

Mar 85

U.S. Department of Commerce
National Technical Information Service
NTIS

PB88-178751

EPA/600/X-85/111
March 1985

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 4,4'-METHYLENEDIPHENYLISOCYANATE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA 22161

TECHNICAL REPORT DATA (Please read Instructions on the reverse before completing)		
1. REPORT NO. EPA/600/X-85/111	2.	3. RECIPIENT'S ACCESSION NO. PB86-178751/AS
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for 4,4'-Methylenediphenylisocyanate		5. REPORT DATE March 1985
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS		10. PROGRAM ELEMENT NO.
		11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		13. TYPE OF REPORT AND PERIOD COVERED
		14. SPONSORING AGENCY CODE EPA/600/22
15. SUPPLEMENTARY NOTES		

16. ABSTRACT

The Health and Environmental Effects Profile for 4,4'-methylenediphenylisocyanate was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for 4,4'-methylenediphenylisocyanate.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a relase as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.

17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 34
	20. SECURITY CLASS (This page) Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
	1.1. STRUCTURE AND CAS NUMBER	1
	1.2. PHYSICAL AND CHEMICAL PROPERTIES	1
	1.3. PRODUCTION DATA	1
	1.4. USE DATA	2
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	4
3.	EXPOSURE	6
4.	PHARMACOKINETICS	7
5.	EFFECTS	8
	5.1. CARCINOGENICITY	8
	5.2. MUTAGENICITY	8
	5.3. TERATOGENICITY	9
	5.4. OTHER REPRODUCTIVE EFFECTS	9
	5.5. CHRONIC TOXICITY	9
	5.6. OTHER RELEVANT INFORMATION	12
6.	AQUATIC TOXICITY	13
7.	EXISTING GUIDELINES AND STANDARDS	14
8.	RISK ASSESSMENT	15
9.	REPORTABLE QUANTITY RANKING (RQ) BASED ON CHRONIC TOXICITY	17
10.	REFERENCES	21
APPENDIX:	LITERATURE SEARCHED	27

LIST OF TABLES

No.	Title	Page
1-1	MDI Production	3
9-1	Composite Scores for the Toxicity of 4,4'-Methylenediphenyl Isocyanate	18
9-2	4,4'-Methylenediphenyl Isocyanate: Minimum Effective Dose (MED) and Reportable Quantity (RQ).	20

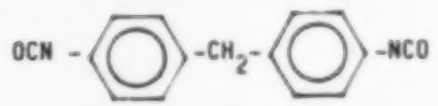
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
CS	Composite score
FEV	Forced expiratory volume
LC_{50}	Concentration lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
MED	Minimum effective dose
ppm	Parts per million
RV_d	Dose-rating value
RV_e	Effect-rating value
TLV	Threshold limit value
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

4,4'-Methylenediphenyl isocyanate (MDI) is also called methylenedi-p-phenyl isocyanate, 1,1'-methylenebis (4-isocyanatobenzene), and diphenylmethane diiso-cyanate. Trade names include Hylene M50 and Isonate. The structural and empirical formulae and CAS registry number are listed below:



Empirical formula: $C_{15}H_{10}N_2O_2$

Molecular weight: 250.3

Chemical Abstracts Service (CAS) Registry Number: 101-68-8

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Some of the physical and chemical properties of MDI are as follows (Woolrich, 1982):

Freezing point:	38°C
Boiling point:	232°C (polymerization)
Vapor pressure:	5×10^{-6} torr at 25°C
Vapor density (air = 1):	8.5

1.3. PRODUCTION DATA

MDI is produced by reacting the parent amines in solution with phosgene at progressively higher temperatures from <60--200°C (Chadwick and Cleveland, 1981). The parent amines are typically 40-60% methylenebis (4-phenylamine), with the remainder mostly other isomers, dimer, trimer and polyamines (SRI International, 1984; Chadwick and Cleveland, 1981). Although MDI has a relatively small share of the market, it is estimated that the growth of rigid foam will result in the MDI group overtaking toluene diisocyanate

(TDI) in volume. MDI is produced by four manufacturers in the United States, listed along with capacities in Table 1-1.

1.4. USE DATA

MDI is used almost exclusively as a monomer for the production of polyurethanes (by the reaction with dihydric alcohols) and other plastics (Chadwick and Cleveland, 1981). Isocyanates in general react with almost any compound having an active hydrogen; the reaction results in an addition to the C=N bond:

$$R - N{=}C{=}O + HA \rightarrow RNHC(O)A$$

When difunctional isocyanates such as MDI react with difunctional active hydrogen compounds, polymers result. The most important of these for MDI are the polyurethane foams produced by reacting MDI with a di- or polyhydric alcohol while foaming the reaction with a blowing agent, usually a fluorocarbon. Tertiary amine or organometal catalysts are always used.

TABLE 1-1

MDI Production*

Manufacturer	Location	Annual Capacity (millions of pounds)
BASF Wyandotte Corp. Polymers Group	Geismar, LA	150
ICI Americas Performance Resins Div.	Geismar, LA	100
Mobay Chemical Corp. Polyurethane Div.	Cedar Bayou, TX	200
	New Martinsville, WV	100
The Upjohn Co. Polymer Chems. Div.	LaPorte, TX	250

*Source: SRI International, 1984

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Virtually no information was found in the available literature (as cited in the appendix) relating to the environmental fate of MDI. Some reports indicate that MDI hydrolyzes relatively rapidly (Woolrich, 1982; Chadwick and Cleveland, 1981); however, no reaction rates were found. In an abstract of a recent paper, Brochhagen and Grieveson (1984) reported that the reaction between MDI and water is relatively slow due to the immescibility of the tested MDI products with water. The resulting reaction products are solid, insoluble, biologically inert polyureas. These products are not degraded easily and do not leach, but apparently show little toxicity to aquatic organisms and bacteria.

Aleksandrova and Tarakanov (1972) presented graphical evidence that the hydrolysis rate constant of 1.33 molar toluene diisocyanate (TDI, a compound similar to MDI) in dioxane was 0.0033 M^{-1} min^{-1}. This yields a half-life of 2.7 hours for 1.33 molar water; although the reaction with MDI is probably on the same order, there is no way to relate this to the environment. Saunders and Frisch (1962) suggested that the rate of airborne TDI reaction could be described by the following empirical relationship:

$$\text{rate} = -k[\text{TDI}][H_2O]^n$$

where n varies from 1 to 2 and k is on the order of 10^{-4} ℓ-sec/mol. For 55.5 molar water, a half-life of ~2 seconds is obtained for n = 1. The applicability of this rate expression to MDI in the environment is not known. These two studies suggest, however, that the liquid phase reaction of MDI with water could be relatively fast. That no reports of ambient MDI levels were found, either in STORET or in the literature, supports the suggestion that MDI reacts relatively rapidly with water, although it must

be emphasized that no data are available that allow the estimation of the hydrolysis rates of MDI under environmentally significant conditions.

Dyson and Hermann (1971) reported that TDI reacts with water vapor in air. Although no reaction rates were given, the authors reported that the reduction in TDI concentration with time was proportional to the relative humidity at constant temperature. Thus, as humidity increased, the TDI removal rate increased. For a 75 second reaction at 50% relative humidity and 75°F, a 33% reduction in the TDI concentration was noted; at 75% relative humidity, a 38% reduction was seen. When TDI concentrations at an 8 second reaction time were compared using a 10-fold initial TDI concentration difference, the absolute reduction in TDI concentrations as found to decrease with decreasing initial concentration. The concentration decrease as a percentage of the initial concentration remained approximately equal, however. Using their data, a half-life of ~13 seconds at 75°F and 50% relative humidity can be calculated for TDI. The reaction for MDI is probably similar.

Based on the reactions of TDI, MDI does not appear to be persistent in the environment, reacting with water with a half-life probably on the order of a few seconds to a few hours. No data are available, however, to directly support this.

3. EXPOSURE

No quantitative data on ambient environmental levels of MDI were found in the available literature (see appendix for literature searched).

4. PHARMACOKINETICS

Pertinent data regarding the absorption, distribution, metabolism and excretion of MDI were not located in the available literature as cited in the appendix.

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of MDI were not located in the available literature as cited in the appendix. MDI is not scheduled for testing by the National Toxicology Program (NTP, 1984).

5.2. MUTAGENICITY

The mutagenicity of synthetic grade MDI, commercial MDI (Caradate 80) and Desmodur E21 (an "MDI type" prepolymerized isocyanate), was evaluated in Salmonella typhimurium by the plate incorporation technique (Andersen et al., 1980). While synthetic grade MDI dissolved in DMSO was not mutagenic in the absence of the rat liver microsomal fraction (S-9) when tested using S. typhimurium strains TA100, 98 and 1537, synthetic grade MDI was mutagenic to strains TA100 and TA98 when incubated in the presence of 150 µl of the S-9 fraction. Both Caradate 80 and Desmodur E21 were mutagenic when tested using TA100 with the addition of S-9. Caradate 80 was almost 7-fold more potent than Desmodur 21 when tested at 50 µg/plate. Caradate 80 was tested at doses up to 100 µg/plate and showed a steep dose response curve up to 50 µg/plate. Desmodur E21 was tested at doses up to 500 µg/plate and showed a much shallower dose response curve.

Foderaro (1978) in an unpublished personal communication reported MDI to be mutagenic in the Ames test. Woolrich (1982) summarized two contradictory unpublished mutagenicity assays. The first tested the mutagenicity of MDI with and without metabolic activation in S. typhimurium (strains TA1535, TA1537, TA1538, TA98 and TA100) at concentrations up to 2500 µg/plate and reported that MDI was mutagenic in strains TA98 and TA100 with metabolic activation. The second tested the mutagenicity of MDI with and without metabolic activation in S. typhimurium (strains TA1535, TA1537, TA1538, TA98

and TA100) and reported that MDI was not mutagenic (Woolrich, 1982). It is not possible to adequately evaluate any of these unpublished studies since only their conclusions are presented.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of MDI were not located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the reproductive effects of MDI were not located in the available literature as cited in the appendix.

5.5. CHRONIC TOXICITY

Pertinent data regarding the effects of subchronic and chronic exposure of animals to MDI were not located in the available literature as cited in the appendix.

Zammit-Tabona et al. (1983) evaluated respiratory function in 1981 in all 78 workers in a foundry where exposure to MDI, measured "around the mold-making area" on two occasions, was found to be 0.08 ppm. The use of MDI (for mold-making) in the foundry started in 1978; a new ventilation system was installed in 1981, shortly after exposure levels were measured and before the workers were evaluated. A "significant increase in the prevalence of respiratory symptoms and lung function abormalities" was observed in exposed workers as compared with a group of unexposed control subjects, but data concerning the nature of the examination and the prevalence of respiratory symptoms and abnormalities among controls were not presented. Of the 78 foundry workers, 12 (15.4%) had symptoms of asthma and evidence of bronchial hyperreactivity as measured by the methocholine challenge test (a screening test for immunologically-induced impaired respiratory function). Further testing was performed on nine of these

hyperreactive individuals and two referred from another foundry where exposure to MDI (level of exposure not reported) occurred. Of these 11 hyperreactive subjects, seven had positive asthmatic reactions resulting in a >20% decrease in FEV when challenge-tested with MDI, implicating MDI as a cause of asthma in these workers. Only one of the seven reacted to formaldehyde, another potential causative agent that was also used in mold-making. Hence, six of the workers reacted specifically to MDI. Asthmatic reactions recurred in four of these six workers for a number of days after the single challenge exposure to MDI and were moderately severe in one. During immunologic studies on these 11 workers, specific IgE antibodies to MDI were detected by the radioallergosorbent test in one worker who responded to MDI challenge and in one who did not respond. Specific IgG antibodies to MDI were detected in two workers who responded to MDI challenge and in two workers who did not respond, one of whom also had MDI-specific PgE. Twenty-four workers of a total of 40 workers reacted to a concentration of 0.02 ppm of MDI, but there did not appear to be any correlation between MDI sensitivity and bronchial reactivity to histamine (Burge, 1982).

Baur et al. (1984) described a case report of a worker occasionally engaged in spraying an MDI/polyol mixture. Average MDI air concentrations were reported as .002-.003 ppm. The worker exhibited a variety of symptoms including fever, leukocytosis and inspiratory rales. The diagnosis of the authors following MDI challenge testing and evaluation of isocyanat specific IgG antibodies was hypersensitivity pneumonitis due to sensitization to MDI.

Musk et al. (1982) measured the effect on the FEV of long-term and short-term exposure to MDI. No effect on the FEV was seen in 107 workers in a polyurethane plastic manufacturing plant over a 5-year period. During the

last year of the study the mean concentration of MDI in the work area was 0.0006 ppm after 193 measurements; 90% of the measured concentration values were $\leq$0.0022 ppm. No effect on the FEV was seen in workers after 2 weeks of vacation from a polyurethane plastic manufacturing plant where the mean concentration of MDI ranged from 0.000-0.003 ppm and the maximum concentration of MDI ranged from <0.003-<0.004 ppm.

Exposure to MDI has been reported to cause dyspnea accompanied by elevated body temperature and leukocyte count (Malo and Zeiss, 1982) within 1 month of exposure. Specific IgG antibodies, which were directed against an MDI human serum albumin conjugate, were identified. Several investigators suggested that there was cross reactivity among the different isocyanates that bound to human serum albumin in eliciting an immune response (Bauer and Fruhmann, 1981; Butcher, 1982; Malo et al., 1983). Although increased production of IgE or IgG (or both) occurred in some of the sensitized workers, increased immunoglobulin production was not associated with most of the workers who developed respiratory distress after occupational exposure to isocyanates (Bauer and Fruhmann, 1981). Bauer and Fruhmann (1981) concluded that exposure to MDI at concentrations >0.01 ppm can elicit nonimmunologic bronchoconstriction. Diller and Herbert (1982) reported that, although decreased, the vital capacity of workers exposed to MDI at concentrations below the maximum permissible levels was not significantly less than nonexposed workers.

MDI exposure has been associated with asthma (Longley, 1964; Munn, 1968; Tanser et al., 1973) and other respiratory impairments, as indicated by the Czech study on the development of stress breathlessness in 19 of 44 workers occupationally exposed to MDI for 16 months (Hassmann, 1973). MDI has also been implicated in chronic obstructive lung disease in 19%, and simple

bronchitis in 21%, of 180 workers exposed to MDI for an unspecified length of time (Sala et al., 1976). Zeiss et al. (1980) reported the development of asthma in one worker and hypersensitivity pneumonitis in another worker after occupational exposure to MDI. Both workers demonstrated serum IgG and IgE against MDI conjugated to human serum albumin but the level was 100-fold higher in the worker who developed hypersensitivity pneumonitis. In addition, the serum of the hypersensitivity pneumonitis patient also contained another precipitating antibody specific for human serum albumin conjugated MDI, which was absent from the serum of the asthma patient (Zeiss et al., 1980). Asthma-type reactions have also been reported in French coal miners exposed to MDI (Bertrand et al., 1984). Also, IARC (1979) reported that human antibody levels (class unspecified) were elevated when workers were exposed to 1.3 ppm/minute (13 mg/m³/minute), but not when exposed to 0.9 ppm/minute (9mg/m³/minute) (Konzen et al., 1966). The presence of circulating immunoglobulins nas not correlated well with an individuals sensitivity to MDI, however, despite the fact that there appears to be immunological cross-reactivity among the different isocyanates, specifically TDI, MDI and hexamethylene diisocyanate (HDI) (Malo et al., 1983; Butcher, 1982).

5.6. OTHER RELEVANT INFORMATION

NIOSH (1978) reported that the LC_{50} for MDI in male rats was 369 mg/m³ for 4 hours and in female rats was 380 mg/m³ for 4 hours.

Lid'en (1980) reported a case of MDI-induced contact dermatitis. Rothe (1976) reported 12 cases of contact eczema in workers exposed to MDI. In vitro inhibition of acetylcholinesterase isolated from human red blood cells and its apparently slow but spontaneous reactivation was described (Dewair et al., 1983). MDI is reported to have slight potential for skin irritation and moderate potential for eye injury when tested in rabbits (NIOSH, 1978).

6. AQUATIC TOXICITY

Pertinent data regarding the acute and chronic toxicity of MDI to aquatic life were not located in the available literature as cited in the appendix.

7. EXISTING GUIDELINES AND STANDARDS

The ACGIH (1983) recommends a TLV of 0.2 mg/m³ (0.02 ppm) for an 8-hour TWA, which is also the ceiling limit for MDI. The Occupational Safety and Health Administration has established a standard for MDI exposure of 0.2 mg/m³ (0.02 ppm) for an 8-hour TWA (Code of Federal Regulations, 1981). Food contact surfaces of polyurethane containers must not contain residues of MDI at concentrations ≥100 ppm (Code of Federal Regulations, 1982).

8. RISK ASSESMENT

Pertinent data implicating MDI as a carcinogen in animals or humans were not located in the available literature as cited in the appendix. Three studies reported that MDI was mutagenic in S. typhimurium (NIOSH, 1978), particularly in strains TA98 and TA100 (Andersen et al 1982; Woolrich, 1982), when incubated in the presence of metabolic activators; one study indicated that MDI was not mutagenic (Woolrich, 1982). No evaluation of the teratogenic and reproductive effects of MDI have been reported, and chronic and subchronic toxicity studies were not located.

Because MDI is widely used in industry, several epidemiological studies exist. However, the available epidemiology studies cannot be used in quantitative risk because, individually or collectively, these studies do not provide data that define a threshold for the action of MDI. In the Zammit-Tabona et al. (1983) study, an increased prevalence of respiratory symptoms and lung function abnormalities was found among workers exposed occupationally to 0.08 ppm MDI, determined on two separate occasions, as compared with the prevalence among unexposed subjects. Twelve of the 78 MDI-exposed workers (15.4%) had symptoms of asthma and responded to a methacholine challenge by increased bronchial hyperreactivity, indicating immunologically-impaired respiratory function. Of that 12, 9 plus 2 referred from another factory were challenged with MDI at a mean concentration of 0.012 ppm for 1 hour, which precipitated a >20% decrease in the FEV of 7 of 11 workers, implicating MDI as a cause of asthma in these workers. Baur et al. (1984) described a case of hypersensitivity pneumonitis due to MDI sensitization following occasional exposure to average MDI concentrations of 0.002-0.003 ppm. In the Musk et al. (1982) study, the FEV of 107 workers

was measured at the beginning and end of a 5-year occupational exposure period and at the beginning and end of a 2-week vacation. No significant changes were observed. The mean MDI concentration in the workplace was 0.0006 ppm, which was measured on 193 different occasions (90% of all the readings were <0.0022 ppm) during the last year of the study.

Exposure to MDI has been shown to cause dyspnea (Malo and Zeiss, 1982) and respiratory distress (Bauer and Fruhmann, 1981), asthma (Longley, 1964; Munn, 1968; Tanser et al., 1973) and other respiratory impairments (Hassmann, 1973). It appears that at least some of the effects of MDI may be consequences of an immune phenomenon (Malo and Zeiss, 1982) that may occur at extremely low levels of exposure. Exposure levels associated with these effects were not provided, and it may well be that these effects occurred at levels less than the apparent NOEL observed by Musk et al. (1982). Because of the deficiencies of these epidemiologic studies and their failure to define a threshold for the action of MDI, an ADI for MDI cannot be calculated.

9. REPORTABLE QUANTITY RANKING (RQ) BASED ON CHRONIC TOXICITY

Inhalation of isocyanates, particularly MDI, can result in impaired respiratory function and the development of asthma (Butcher, 1982; Bauer and Fruhmann, 1981; Longley, 1974; Munn, 1968; Tanser et al., 1973; Zammit-Tabona et al., 1983). No chronic or subchronic toxicity studies in animals have been located in the available literature. Occupational exposure at a level of 0.08 ppm of MDI, however, resulted in symptoms of asthma and bronchial hyperreactivity in 15.4% of exposed workers (Zammit-Tabona et al., 1983). Further testing of 11 exposed workers who had developed asthma indicated that MDI was the causative agent for six (see Section 5.5. for details). In these sensitized individuals challenge exposures of 0.012 ppm for 1 hour were sufficient to decrease FEV in 7 of the 11 affected works. In addition, Baur et al. (1984) reported hypersensitivity pneumonites in a worker exposed to an average of 0.002-0.003 ppm MDI.

The data base for MDI dose/effect evaluations is extremely weak. It appears that in sensitive individuals, adverse effects may occur following exposure to extremely low concentrations of MDI. For these reasons, it is considered that the available data are inadequate to support adjustment of the RQ based on chronic toxicity.

The exposure in ppm (0.08) from Zammit-Tabona et al. (1983) corresponds to 0.8192 mg/m³. The human MED for a 70 kg man is derived from the occupational exposure level by multiplying the effective exposure level (0.8192 mg/m³) by the average volume of air ventilated during an 8-hour work shift (10 m³/day), and converting the effective exposure level to the equivalent average continuous exposure level by multiplying by the number of days worked per week (5/7) to give a value of 5.85 mg/day (Table 9-1).

TABLE 9-1

Composite Scores for the Inhalation Toxicity of
4,4'-Methylenediphenyl Isocyanate*

Species	Dose/Exposure	Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ
Human	0.08 ppm (0.8192 mg/m³) 8 hours/day 5 days/week	5.85	4.35	Symptoms of asthma, bronchial hyper-reactivity	9	39.2	ND

*Source: Zammit-Tabona et al., 1983

ND = Not derived

The RV_d corresponding to an MED of 5.85 mg/day is 4.35 (Table 9-2). Because asthma results in pronounced pathological changes accompanied by severe lung dysfunction, an RV_e value of 9 was assigned. The CS, which is the product of the RV_d and the RV_e, is 39.2, an RQ is not estimated.

TABLE 9-2

4,4'-Methylenediphenyl Isocyanate

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose:	5.85 mg/day
Effect:	symptoms of asthma, bronchial hyperreactivity
Reference:	Zammit-Tabona et al., 1983
RV_d	4.25
RV_e	9
Composite Score	39.2
RQ	ND

ND = Not derived

10. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1983-1984. ACGIH, Cincinnati, OH. p. 25.

Aleksandrova, Yu.V. and O.G. Tarakanov. 1972. Some kinetic relationships of the water - isocyanate reaction. Vysokomol. Soyed. A14: 23-29.

Andersen, M., M-L. Binderup, P. Kiel, H. Larsen and J. Maxild. 1980. Mutagenic action of isocyanates used in the production of polyurethanes. Scand. J. Work Environ. Health. 6(3): 221-226.

Andersen, M., M-L. Binderup, P. Kiel, H. Larsen and J. Maxild. 1982. Mutagenic action of isocyanates used in the production of polyurethanes. Reply to comments. Scand. J. Work, Environ. Health. 8: 80-81.

Baur, X. and G. Fruhmann. 1981. Specific IgE antibodies in patients with isocyanate asthma. Chest. 80(1): 73-76.

Baur, X., M. Dewair and H. Rommelt. 1984. Acute airway obstruction followed by hypersensitivity pneumonitis in an isocyanate (MDI) worker. J. Occup. Med. 26: 285-287.

Bertrand, J.P., J.M. Wantz, P. Heintz and M. Zitter. 1984. Pathology linked with the use of isocyanates in the coal mines of Lorraine. Arch. Mal. Prof. Med. Trav. Secur. Soc. 45(1): 3-9. (Cited in CA 101:11676e)

Brochhagen, F.K. and B.M. Grieveson. 1984. Environmental aspects of isocyanates in water and soil. Cell. Polym. 3(1): 11-17.

Burge, P.S. 1982. Non-specific bronchial hyper-reactivity in workers exposed to toluene di-isocyanate, diphenyl methane di-isocyanate and colophony. Eur. J. kespir. Dis. 123: 91-96.

Butcher, B.T. 1982. Isocyanate induced asthma. Eur. J. Respir. Dis. 123: 78-81.

Chadwick, D.H. and I.H. Cleveland. 1981. Isocyanates, Organic. In: Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 13, 3rd ed., M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc. p. 789-818.

Code of Federal Regulations. 1981. OSHA Safety and Health Standards. 29 CFR 1910.1000.

Code of Federal Regulations. 1982. Polyamide-imide resins (57,047.5). 21 CFR 177.2450 (7-26-82).

Dewair, M., X. Baur and R. Mauermayer. 1983. Inhibition of acetylcholin-esterase by diisocyanates and its spontaneous reactivation. Int. Arch. Occup. Environ. Health. 52(3): 257-261.

Diller, W.F. and E. Herbert. 1982. Lung function and other health parameters in isocyanate plant workers (diphenylmethane diisocyanate (MDI) manufacturing). Zentralbl. Arbeitsmed. Arbeitsschutz. Prophyl. Ergon. 32(4): 128-132. (Cited in CA 98:148925z)

Dyson, W.L. and E.R. Hermann. 1971. Reduction of atmosphereic toluene diisocyanate by water vapor. Am. Indust. Hygiene Assoc. J. 32: 741-744.

Foderaro, J. 1978. Written communication (June, 1978) quoted by the U.S. Institute for Occupational Safety and Health. In: National Institute for Occupational Safety and Health. Criteria for a Recommended Standard Occupational Exposure to Diisocyanates. Cincinnati, OH. (Cited in Andersen et al., 1982)

Hassmann, P. 1973. The health status of workers with diphenylmethane 4,4'-diisocyanate (MDI) (Czeck.) Pracov. Lik. 25: 242-244. (Cited in IARC, 1979)

IARC (International Agency for Research on Cancer). 1979. In: Some Monomers, Plastics and Synthetic Elastomers and Acrolein. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyon, France. 19: 315-320.

Konzen, R.B., B.F. Craft, L.D. Scheel and C.H. Gorski. 1966. Human response to low concentrations of p,p-diphenylmethane diisocyanate (MDI). Am. Ind. Hyg. Assoc. J. 27: 121-127. (Cited in IARC, 1979)

Lid'en, C. 1980. Allergic contact dermatitis from 4,4'diisocyanatol-diphenyl methane (MDI) in a molder. Contact Dermatitis. 6(4): 301-302.

Longley, E.O. 1964. Methane diisocyanate: A respiratory hazard? Arch. Environ. Health. 8: 898. (Cited in IARC, 1979)

Malo, J.L. and C.R. Zeiss. 1982. Occupational hypersensitivity pneumonitis after exposure to diphenylmethane diisocyanate. Am. Rev. Respir. Dis. 125(1): 113-116.

Malo, J.L., G. Ouimet, A. Cartier, D. Levitz and C.R. Zeiss. 1983. Combined alveolitis and asthma due to hexamethylene diisocyanate (HDI), with demonstration of crossed respiratory and immunologic reactivities to diphenylmethane diisocyanate (MDI). J. Allergy Clin. Immunol. 72(4): 413-419.

Munn, A. 1968. Health hazards from isocyanates. Adv. Polyurethane Technol. 16: 299-301. (Cited in IARC, 1979)

Musk, A.W., J.M. Peters, L. DiBerardinis and R.L.H. Murphy. 1982. Absence of respiratory effects in subjects exposed to low concentrations of toluene diisocyanate and diphenylmethyldiisocyanate. J. Occup. Med. 24(10): 746-750.

NIOSH (National Institute for Occupational Safety and Health). 1978. Criteria for a Recommended Standard...Occupational Exposure to Diisocyanates. Publ. No. 78-215. U.S. DHEW, PHS, CDC, Rockville, MD.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program Management Status Report. 10/25/84.

Rothe, A. 1976. [Occupational skin diseases caused by polyurethane chemicals.] Berufs-Dermatosen. 24: 7-24. (Cited in NIOSH, 1978)

Saia, B., L. Fabbri, C. Mapp, G. Marcer and G. Mastrangelo. 1976. Epidemiology of chronic non-specific lung disease in a population exposed to isocyanate. I. Analysis of symptoms. Med. Lav. 67: 278-284. (Cited in IARC, 1979)

Saunders, J.H. and K.D. Frisch. 1962. Polyurethanes: Chemistry and Technology. Part I. Interscience Publishers, NY. p. 182. (Cited in Dyson and Hermann, 1971)

SRI (Stanford Research Institute) International. 1984. Directory of Chemical Producers: United States of America. SRI International, Menlo Park, CA. p. 660.

Tanser, A.R., M.P. Bourke and A.G. Blandford. 1973. Isocyanate asthma: Respiratory symptoms caused by diphenyl-methane diisocyanate. Thorax. 28: 596-600. (Cited in IARC, 1979)

Woolrich, P.F. 1982. Toxicology, industrial hygiene and medical control of TDI, MDI and PMPPI. Am. Ind. Hyg. Assoc. J. 43(2): 89-97.

Zammit-Tabona, M., M. Sherkin, K. Kijek, H. Chan and M. Chan-Yeung. 1983. Asthma caused by diphenylmethane diisocyante in foundry workers. Am. Rev. Respir. Dis. 128(2): 226-230.

Zeiss, C.R., T.M. Kanellakes, J.D. Bellone, D. Levitz, J.J. Pruzansky and R. Patterson. 1980. Immunoglobulin E-mediated asthma and hypersensitivity pneumonitis with precipitating anti-hapten antibodies due to diphenylmethane diisocyanate (MDI) exposure. J. Allergy Clin. Immunol. 65(5): 347-352.

APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in November, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. p. 486.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1983-1984. Cincinnati, OH. p. 94.

BCPC (British Crop Protection Council). 1977. Pesticide Manual, 5th ed., H. Martin and C.R. Worthing, Ed. British Crop Protection Council. p. 593.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. p. 2878.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-83. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. p. 575.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. p. 700.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Management Status Report.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1983. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1982. Chemical Activities Status Report, 3rd ed. (EPACASR). Offices of Pesticides and Toxic Substances, Washington, DC. EPA 560/TIIS-82-002b.

U.S. EPA. 1983. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call In Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1984. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (United States International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982. Washington, DC. USITC Publ. 1422.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.